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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,543	11/07/2005	John Donnelly	PP019844.0003	4724

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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,543	DONNELLY ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *7-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received June 16, 2008.

Election/Restrictions

Applicant's election with traverse of Group I claims 1-6 is acknowledged. Applicants argue that independent claim 14 recites all the elements present in claim 1 and claim 7. Applicants provide a table summarizing the components of the compositions of Groups I, II, III and IV. Applicants argue that examination of Group IV will necessarily include an examination of Groups I, II, and III. In response, the Office respectfully disagrees with Applicant's contention. In the restriction requirement of 2/19/2008 the Office cited prior art document, US Patent 7,211,659 B2 disclosing the shared technical feature of the present invention. Additionally US Patent 6,753,015 and O'Hagan et al. (Journal of Virology, October 2001, Vol. 75, p. 9037-9043) disclose the technical feature of the invention as discussed under art rejections below. Because Applicant's invention does not contribute a special technical feature when viewed over the prior art, the claims do not relate to a single inventive concept and therefore lack unity of invention. Were this application subject to US restriction practice, combination/subcombination analysis would apply and the restriction would still be proper. If all the claims in Group I are found to be allowable, the examiner will consider rejoinder of Group IV. The restriction is deemed proper and is made FINAL.

Claims 1-6 and new claims 40 and 41 are under examination in this Office Action. Claims 7-39 are withdrawn because they are drawn to non-elected invention.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/7/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HIV DNA **immunogenic composition**, does not reasonably provide enablement for an HIV **vaccine**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claims are drawn to an HIV DNA vaccine composition comprising a nucleic acid expression vector expressing HIV Gag or HIV Env, and comprising PLG. The claims are rejected because the specification does not provide sufficient enablement for the claimed vaccines.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors deemed relevant are those of the amount of direction and the working examples provided, that quantity of experimentation necessary, the (un) predictability of the art, and the breadth of the claims.

Claims are drawn to an HIV DNA vaccine composition comprising a nucleic acid expression vector expressing HIV Gag or HIV Env, and further comprising PLG microparticles. The term "vaccine" by definition implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease.

The specification describes animal studies in BALB/c mice and rabbits evaluating the toxicity of the claimed composition (Example 4). Example 6 provides information with regard to the safety of the MF59 adjuvant in humans and proposes a protocol for the study of the claimed composition in humans. Example 5 describes immunization of rhesus monkeys with the composition of the invention and studying of the immune responses. The specification does not provide scientific data with regard to challenge experiments in vaccinated subjects.

There is insufficient evidence that the vaccinated monkeys are protected from HIV infection. There is insufficient evidence that the study proposed in Table 19 would show that the claimed composition can indeed be useful as vaccine to protect humans from HIV infection.

It is well known in the art that retroviral therapies, especially HIV therapies, are refractory to anti-viral therapies (see Letvin, 2006, Nature Immunology, Vol. 6, p. 930-939). The obstacles to developing a successful therapy of HIV are well documented in the literature. These obstacles include 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with the respect to the gene encoding the envelope protein. 2) The fact that the mode of viral transmission includes both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission. 3) The establishment of a latent viral infection. 4) The ability of the virus to evade the immune responses in the central nervous system due to the blood-brain barrier. 5) The complexity and variation of the pathology of HIV infection in different individuals. 6) The inability of a natural infection to one strain of HIV to protect an individual from being infected with another strain of HIV (Machuca et al. Intervirology 1999, Vol. 42 p. 37-42, see discussion). These obstacles establish that the contemporary knowledge in the art would not allow one of skill in the art to use the claimed vaccine to treat and/or prevent HIV infection without undue experimentation. Furthermore, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion.

Applicants have not provided any convincing evidence that their claimed vaccine is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient

guidance in to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Hagan et al. (Journal of Virology, October 1, 2001, Vol. 75, p. 9037-9043).

Claims are drawn to an HIV DNA vaccine composition comprising a nucleic acid expression vector comprising at least one HIV Gag or Env encoding sequence and PLG. The present specification discloses that PLG is a poly-lactide-coglycolide microparticle. The concentration of PLG is between about 5 and 100 fold greater than the concentration of the nucleic acid expression vector. The concentration of nucleic acid is between about 10 μg/mL and 5 mg/mL and the concentration of the PLG is between 100 μg/ml and 100 mg/ml. The nucleic acid concentration per dose is between approximately 1 μg/dose and 5 mg/dose and the PLG concentration is between approximately 10 μg/dose and 100 mg/dose. The composition further comprises an adjuvant.

The claims are rejected for the enabled immunogenic composition.

O'Hagan et al. disclose a composition comprising a nucleic acid expression vector encoding HIV Gag, PLG a poly-lactide-coglycolide microparticle, and a MF59 adjuvant (see the entire document, particularly Materials and Methods: DNA plasmids, Preparation of PLG microparticles, and page 9039). O'Hagan et al. disclose that the DNA was absorbed onto the PLG particles by incubating 100 mg PLG particles in 1 mg/ml of DNA solution (see Preparation of PLG particles on page 9038). Thus O'Hagan's concentration of PLG is 100 fold greater than the concentration of the nucleic acid expression vector. O'Hagan's PLG concentration is 100 mg/ml and nucleic acid concentration is 10 mg/ml –both within the claimed ranges. O'Hagan disclose a single dose of 1 and 10 μg HIV Gag DNA (1000 ng = 1 μg and 10 000 ng = 10 μg) and a single dose of 10 μg PLG (see Table 1 and page 9039). By this disclosure O'Hagan anticipate the present claims.

Claims 1-3 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Fang et al. (US Patent 6,753,015).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Fang et al. disclose compositions comprising PLG microparticles and nucleic acid expression vectors expressing HIV Gag and Env, and an adjuvant (see claims 1-5 and 11-19).

Fang et al. disclose that the DNA was absorbed onto the PLG particles by incubating 100 mg PLG particles in 1 mg/ml of DNA solution (see Examples 4 and 7), thus Fang's concentration of PLG is 100 fold greater than the concentration of the nucleic acid expression vector. Fang's PLG concentration is 100 mg/ml and nucleic acid concentration is 10 mg/ml –both within the claimed ranges. By this disclosure Fang et al. anticipate the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 6 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan et al. (Journal of Virology, October 1, 2001, Vol. 75, p. 9037-9043) in alternative over Fang et al. (US Patent 6,753,015) as applied to claim 1 and further in view of Krieg et al. (US Patent Application Publication 20030050263 A1) and Langermann et al (US Patent Application Publication 2003/0199071 A1).

O'Hagan et al. and Fang et al. teach compositions comprising PLG microparticles, nucleic acid expression vector expressing HIV Gag and Env and an adjuvant, as discussed above. O'Hagan teaches that the concentration of PLG is between 5 and 100 fold greater than the concentration of DNA. Fang teach that his composition comprises hexadecyltrimethylammonium bromide, EDTA and sodium citrate dehydrate and citric acid (see claim 10, column 6, lines 14-22, and Examples 5 and 6). However neither O'Hagan nor Fang teach a composition comprising 50.0 mg/ml PLG, 2.0 mg/ml plasmid DNA, 0.5 mg/ml hexadecyltrimethyulammonium bromide,

0.37 mg/ml EDTA, 1.4 mg/ml sodium citrate dehydrate, 0.04 mg/ml citric acid monohydrate, 44 mg/ml mannitol or 14.7 mg/ml sucrose.

While O'Hagan teaches MF-59 adjuvant, O'Hagan does not teach the components of the MF-59 adjuvant such as 39 mg/ml squalene, 4.7 mg/ml polysorbate 80, 4.7 mg/ml sorbitan trioleate, 2.68 mg/ml sodium citrate dehydrate, and 0.17 mg/ml citric acid monohydrate.

However, it would have been obvious to the skilled artisan to provide O'Hagan's and Fang's composition further comprising Krieg's mannitol and sucrose, because Krieg teach that compositions comprising nucleic acids for anti-HIV therapy, particularly the compositions for oral administration can be formulated with mannitol and sucrose as pharmaceutical carriers (see [0138]). It would have been obvious to provide the claimed amounts of mannitol and sucrose, because these pharmaceutical carriers are routinely used as components of compositions for administration in humans.

It would have been *prima facie* obvious to adjust the amounts of all carrier components of the claimed composition, because all components have been known and used in the art as discussed above. Absent any unexpected results, it would have been a routine optimization to adjust the amounts of the carrier components of the present composition. It would have been *prima facie* obvious to provide a composition comprising 50.0 mg/ml PLG, 2.0 mg/ml plasmid DNA because O'Hagan teaches that the concentration of PLG should be 5 to 100 fold grater than the concentration of the nucleic acid (see Preparation of PLG particles on page 9038 and Table 1). Absent any unexpected results, it would have been a routine optimization to provide the claimed concentrations of nucleic acid and PLG.

With regard to claim 41 drawn to specific components of the adjuvant, the present specification discloses that the 39 mg/ml squalene, 4.7 mg/ml polysorbate 80, 4.7 mg/ml sorbitan trioleate, 2.68 mg/ml sodium citrate dehydrate, and 0.17 mg/ml citric acid monohydrate are the components of the MF59C.1 adjuvant (see table 4). The MF59C.1 adjuvant has been known and used at the time of the present invention. Langermann et al. teaches an MF59.1 adjuvant comprising 39 mg/ml squalene, 4.7 mg/ml polysorbate 80, 4.7 mg/ml sorbitan trioleate, 2.68 mg/ml sodium citrate dehydrate, and 0.17 mg/ml citric acid monohydrate (see [0159]). It would have been obvious to use Langermann's adjuvant in the composition of Fang and O'Hagan because MF59C.1 adjuvant has been shown to effectively contribute to generation of antigen specific immune responses as evidenced by Langermann.

One would have had a reasonable expectation of success to optimize the amounts of the carrier components of the claimed composition and to use the MF59C.1 adjuvant because the claimed carrier components and the MF59C.1 adjuvant have been known and routinely used in the art as evidenced by the Krieg and Langermann.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/
Examiner, Art Unit 1648

/Bruce Campell/
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